EXHIBIT 4

TO: Charles Schwamlein, M.D., M.P.H.
Kenneth W. Sommerville, M.D., FAAN
Abbott Laboratories
Abbott Park, IL 60064

FROM: Lewis B. Holmes, M.D., Director
Diego F. Wyszynski, M.D., Ph.D., Epidemiologist
Maya Nambisan, M.P.H., Coordinator
Kristin Morales, Data Analyst

RE: Findings in pregnancies in which the infant had been exposed to valproic acid (brand names Depakote, Epival)

DATE: August 30, 2002

The Scientific Advisory Committee of the AED (anticpileptic drug) Pregnancy Registry has authorized the release to your company of the information obtained to date from pregnancies in which the newborn infant had been exposed to Depakote, a product of Abbott Laboratories. It is the policy of the Registry to inform each manufacturer of a drug about the findings prior to the release of the information to the public. That release will be in an abstract submitted to the annual meeting (February 3 – 8, 2003 in San Francisco) of the Society for Maternal Fetal Medicine.The abstract will be published in a supplement issue of the American Journal of Obstetrics and Gynecology, most likely in January, 2003.

A major goal of the AED Pregnancy Registry is to identify anticonvulsant drugs which have a harmful effect on the fetus. The primary outcome looked for is major malformations, which are defined as structural abnormalities with surgical, medical, or cosmetic importance.

The Scientific Advisory Committee has established criteria for the release of information to the scientific community and the public. When it became clear at the Registry's semiannual meeting on June 5-6, 2002 that these criteria had been met among infants exposed to valproate, the decision was made to contact you as the representative of the manufacturer.

The members of the Scientific Advisory Committee are:

Joseph Bruni, M.D.
Neurologist, Wellesley Hospital
Toronto, Canada

Janet Cragan, M.D.
Birth Defects Branch,
Obstetrician
Centers for Disease Control
Atlanta, GA

Allen Hauser, M.D.
Department of Neurology
Columbia-Presbyterian Hospital
New York, NY

Lewis B. Holmes, M.D.
Director, AED Pregnancy Registry,
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Massachusetts General Hospital
Boston, MA

Ms. Margaret Jacobs
Program Director
Epilepsy Branch, NIH

Robert Mittendorf, M.D., Dr.P.H.
Epidemiologist and
Loyola University
Chicago, IL

Mark Yerby, M.D. (Chair)
Neurologist
Portland, OR

All members, except Dr. Bruni, were present at the meeting in June.

The present report was developed by the staff of the AED Pregnancy Registry:

Lewis B. Holmes, M.D.	Director and Teratologist
Diego F. Wyszynski, M.D., Ph.D.	Epidemiologist
Maya Nambisan, M.P.H.	Coordinator
Sabrina Petersen	Program Assistant
Kristin Morales	Data Analyst
Edward Bromfield, M.D. Daniel Hoch, M.D., Ph.D. Shahram Khoshbin, M.D.	Epileptologists
Joan Stoler, M.D.	Staff Physician
Rosanna Greco	Secretary

Lois Parker, R.Ph. Pharmacy Liaison

We attach copies of the NIH-style biosketches of Drs. Holmes and Wyszynski.

If after reviewing this report you would like to have additional information on these exposed pregnancies and the fetal effects, please contact Dr. Holmes, Director of the AED Pregnancy Registry,at the following address:

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To facilitate the reading of this report, we provide background information about the Registry and the criteria that have been established for the release of findings, as well as the results and a summary of previous observations of the birth defects in infants exposed *in utero* to valproic acid.

I. BACKGROUND

The AED Pregnancy Registry was established at the Massachusetts General Hospital in Boston in December, 1996. It was supported during the first two years by funds provided by six companies which manufacture and market an anticonvulsant: Abbott Laboratories, GlaxoWellcome, Hoechst-Marion-Roussel, Novartis, Ortho-McNeil, and Parke-Davis. During the next three years the same companies, except for Hoechst-Marion-Roussel, were sponsors; in addition, UCB Pharma made a donation in the fourth year. Parke-Davis and GlaxoWellcome have merged with other companies and have been renamed Pfizer and GlaxoSmithKline, respectively.

Representatives of each company constitute the Steering Committee which meets every six months with the Scientific Advisory committee. (However, the decisions about releasing information on a drug are made independently by the Scientific Advisory Company at a separate meeting.) The current members of the Steering Committee are:

ABBOTT:	Kenneth Sommerville, M.D. Charles Schwamlein, M.D., M.P.H.
GLAXOSMITHKLINE:	Patricia Tennis, Ph.D.*

NOVARTIS:	Javier Cid, M.D., M.P.H., Dr.PH
ORTHO-MCNEIL:	Daniel Fife, M.D., Ph.D. Joseph Hulihan, M.D.
PFIZER:	Cathy Sigler, D.V.M., Ph.D.
ELAN PHARMACEUTICALS:	Wendy Martin, M.D. Randall D. Fong, R.Ph., M.S.

The goal of the Registry is to determine, from the outcomes of the pregnancies of each enrolled woman, the health status of her infant, with a particular focus on the occurrence of any major malformations. There are several steps:

1. the woman calls the toll-free number (1-888-233-2334) to ask about the study; if she is interested, she is sent by mail an informed consent document and a stamped return envelope; she must call, as part of the informed consent process; her doctor cannot enroll her;

2. a 12-minute interview at enrollment to determine the medication she is taking, information about her epilepsy (or any other condition for which she is taking an anticonvulsant), other exposures (alcohol, smoking, etc.) and demographic characteristics;

3. an interview at 7 months gestation to confirm her address and telephone number (about 10% have changed), to determine whether she has changed her medication and any fetal abnormalities identified by prenatal screening;

4. at 4 to 8 weeks after the woman's expected date of delivery, she is contacted to ask about the health status of her infant; with her written permission, information is obtained about the findings in her infant by her infant's pediatrician or family practitioner and about her health status with reports from her neurologist;

5. the findings in each interview and from the reports received are abstracted for data entry in a format that facilitates tabulation and analysis.

Explicit criteria have been established for determining which outcomes are a major malformation and what physical findings are to be excluded. The definition of a major malformation, cited above ("a structural abnormality with surgical, medical or cosmetic importance"), has been used by Dr. Holmes in directing the Active Malformations Surveillance Program at Brigham and Women's Hospital. Since 1972, this program has identified all infants with major malformations among over 200,000 births. The methodology and the findings in the first ten years were described by Nelson and Holmes in New England J Medicine 320:19-23, 1989.

From this experience,inclusion and exclusion criteria for major malformations were developed which have been used by the Registry. The physical features excluded are: minor anomalies, birth marks, deformations, physiologic features of prematurity (such as patent ductus arteriosus [PDA]), and malformations due to either chromosome abnormalities or dominant or recessive genes. These criteria are critical, as experience has shown that the physical outcomes excluded are much more common than major malformations. A discussion by Dr. Holmes of these inclusion and exclusion criteria was published in Teratology (59:1-2, 1999).

A woman is classified as having enrolled *prospectively* if at the time of enrollment she has no knowledge of the health status of her unborn infant. This includes all women enrolling before 16 weeks of gestation, the time chosen as the earliest time in pregnancy when structural abnormalities are likely to be detected. We designate this group in the report (below) as "pure prospective". We also include in this group women who at enrollment have had prenatal screening, such as ultrasound that could have identified a fetal abnormality. We have designated separately this group "impure prospective," for lack of a better term.

Many pregnancy registries designate a "retrospective" group, which is composed of women whose unborn infants have been found to have major malformations by prenatal testing. We do not enroll this group in the AED Pregnancy Registry. Likewise, we do not enroll women who call the Registry after their pregnancy has ended.

As of April 30, 2002, more than 2,900 women had enrolled in the Pregnancy Registry.

II. GUIDELINES FOR DATA ANALYSIS AND PUBLICATION FOR THE AED PREGNANCY REGISTRY

The Scientific Advisory Committee developed and approved the following guidelines at its meeting on June 5, 2002:

1. The population of enrolled women whose pregnancy outcomes will be used to determine the release of findings represents "pure prospective cases," meaning that the woman enrolled at 16 weeks or less of gestation (GA) and does not know the health status of her drug-exposed infant. If a woman has had an earlier prenatal screening test, such as chorionic villus sampling (CVS) at 10 or 11 weeks GA or measurement of nuchal translucency at 12 weeks, she will not be considered "pure" prospective.

   Women who enroll at 16 weeks GA or thereafter and whose prenatal screening did not identify a fetal abnormality will be enrolled, and designated separately. A suitable term for this group, i.e. "impure" prospective, has not been determined.

   Women whose drug-exposed fetus has been found by prenatal screening to have a significant major malformation will not be enrolled as a prospective case or included in the analysis of the findings.

2. Primary outcome to be studied will be major malformations. Inclusion and exclusion criteria for major malformations have been defined by and are the same as have been used in the Active Malformations Surveillance Program at Brigham and Women's Hospital.

3. The comparison group used for initial analyses will be the data from the Active Malformations Surveillance Program at Brigham and Women's Hospital. The overall prevalence of malformations in this population in the first ten years was 1.62%, after excluding infants with chromosome abnormalities and recognized genetic disorders.

4. Publication of results for a positive association (RR>1) will occur when the lower confidence limit is 2.0 or higher. In this way, we will be 95% confident that there is at least a two-fold increase.

   Publication for drugs with no association, publication will occur when the upper confidence limit does not exceed 2.0. This will allow us to say with 95% confidence that the increase in risk is not greater than 50%.

III. ISSUES ON STATISTICAL POWER

An important feature of the AED Pregnancy Registry is its ability to detect whether malformations occur at a different rate among women receiving AEDs compared with women not receiving a AEDs. This determination is made for the overall group of AEDs (any drug vs. no drug) as well as for specific drugs.

Thestatistical power of the Registry is its ability to detect a difference in the prevalence of malformations between groups,assuming such difference actually exists. Power can range from 0 to 100%; a higher number indicates better ability to detect true differences. The statistical power of the Registry is influenced by both the number of subjects enrolled and by the strength of the association under study. The larger the difference in the prevalence of malformations one is trying to detect, the smaller the number of subjects needed to detect the difference. (For example, many fewer subjects would be needed to detect a 20-fold increase in risk than to detect 2-fold increase). Similarly, the more subjects enrolled, the greater the ability of the Registry to detect relatively smaller increases in the prevalence of malformations.

Commonly, 80% power to detect specific associations of interest is considered acceptable. This level of power means that if an association exists (e.g., a 5-fold increase in the prevalence of heart defects among women on a specific drug compared to women not taking drugs), the Registry would detect that association 80% of the time. Conversely, 20% of the time the registry would not detect such an association even though it really exists. Power can be a particularly difficult issue in studying congenital malformations (and particularly specific malformations) because malformations occur relatively rarely and, therefore, large sample sizes are needed. For example, for a statistical power of 80%, alpha = 0.05, and a relative risk of 2.0, 555 drug-exposed

pregnancies would bethe minimum sample size necessary to detect a true association. Given the rarity of the anomalies collected by the Registry,they are pooled into a single "major congenital anomaly group." Under this strategy, a projection of 555 collected cases is realistically attainable.

IV. RESULTS

Between February, 1997 and May, 2002, the total number of enrolled women was 2918. We present here the findings in 1184 "pure" and 902 "impure" prospective enrollees whose infants have been born and for whom we have outcome resultsThe total number in each group isreduced by spontaneous abortions, elective terminations, and women who were lost to follow-up (in spite of intense efforts to locate). Table 1 shows the distribution of the outcomes of the pregnancies stratified by "pure" and "impure" status.

Table 1. Outcome of the pregnancy by "pure"/"impure" status.

	"Pure" Prospective		**"Impure" Prospective**	
	Total Registry	Depakote	Total Registry	Depakote
Spontaneous abortion	41	8	2	-
Elective termination	9	1	1	-
Stillbirths, neonatal deaths	5	4	6	-
Lost to follow-up	79	11	52	8
Livebirths	1030	118	835	78
Total number	**1181**	**142**	**902**	**86**
Total available for analysis	1044	**123**	**842**	**78**

A spontaneous or elective termination would be included as an abnormal outcome if information was available from an autopsy. None was available for any of these products of conception. Infants who were exposed to Depakote monotherapy and who died in the neonatal period (3) or were stillborn (1) were included in the samples analyzed because information was available on their health status and the presence/absence of major malformations. Information on elective terminations because of fetal abnormalities, stillbirths and neonatal deaths were included in the comparison population at Brigham and Women's Hospital.

Tables 2 and 3 present exposure information and clinical characteristics of the 17 newborns with congenital anomalies whose mothers usedvalproate monotherapy. Two twin siblings (#1181a and b) were exposed to Epival, a product of Abbott Laboratories sold in Canada; all other infants with major malformations were exposed to the drug Depakote.

Table 2. Clinical characteristics of newborns exposed to valproate monotherapy.

Congenital Malformation	Number of Cases	Comments
Heart defects****	6	Includes one infant with heart defects and forearm deformities.
Spina bifida***	4	Two affected fetuses were twins; one infant with spina bifida had also an associated cleft palate.
Hypospadias*	2	Moderate to severe, penile or penoscrotal location
Multicystic dysplastic kidneys, bilateral*	1	Lethal malformations of kidneys, bilateral; pregnancy terminated
Cleft lip and palate	1	
Inguinal hernia*	1	Diagnosed at 8 days of age
Polydactyly, postaxial*	1	
Cleft foot*	1	
Total	17	

The number of stars (*) indicates the number of malformations occurred in "pure prospective" pregnancies

The heart defects are notable because two were rare and severe malformations: 1) participant #1085 has a tetralogy of Fallot with pulmonary atresia; 2) participant#3445 had pulmonary atresia, tricuspid valve stenosis and ventricular septal defect (this infant died, in spite of reparative surgery, at 12 days of age).
Three infants have multiple malformations: #1078, #2414, and #3060.

Table 3. Exposure information and clinical characteristics of newborns exposed to valproate monotherapy.

Case Number	Dosage at Conception (mg)		Amount of Dosage Change (mg) and Time of Change	Birth Status	Major Malformation
	Mother's Report	Medical Records			
1078 (Impure)	1500	2500	0	Live	Patent Ductus Arteriosus, Trigonocephaly, Hypospadias [Penile], Dysmorphic Face, 46, XY
1085 (Pure)	1000	1000	250 at 19 weeks	Live	Tetralogy of Fallot, Pulmonary Atresia

1181a and b (Pure)	Epival 1000	Epival 1000	0	Pregnancy Terminated at 18 Weeks	Twins with spina bifida
1465 (Impure)	1125	1125	125 Last 2 Weeks of Pregnancy	Live	Hypospadias (Penile)
2118 (Pure)	1000	1000	500 at Week 25	Live	Atrial Septal Defect, Bicuspid Aortic Valve
2321 (Pure)	500	500	0	Live	Polydactyly, Postaxial, Type B
2326 (Impure)	1500	1500	0	Live	Atrial Septal Defect, Hypoplastic Radius (Bilateral)
2364 (Pure)	750	750	750 in 3rd trimester	Live	Inguinal Hernia (Bilateral)
2414 (Pure)	2000	2000	250 at 7 months	Live	Spina Bifida, Cleft Palate
2547 (Pure)	1500	1500	0	Live	Hypospadias, (Penoscrotal)
2712 (Pure)	1250	No Pediatric Records	0	Live	Ventricular Septal Defect
2978 (Pure)	750	No Pediatric Record	0	Live	Equinovarus Club Foot Deformity
2997 (Pure)	750	Refused Records	From 750 - 0 in 3rd Trimester	Pregnancy Terminated	Multicystic Dysplastic Kidneys, Bilateral
3060 (Impure)	1500	1500	0	Live	Spina Bifida (Lumbosacra), Hemangioma on Cheek
3445 (Pure)	250	250	Started at 500; 1000 at 3 Wks; 250 at 6 Wks	Neonatal Death at 12 days of age	Pulmonary Atresia, VSD, Tricuspid Valve Stenosis
3515 (Impure)	750	No records	0	Live	Cleft Lip and Palate

As stated in section II, we compared the major malformation prevalence rate for women exposed to valproate to that of women participating in the Active Malformations Surveillance Program at Brigham and Women's Hospital (overall prevalence of malformations =1.62%, after excluding infants with chromosome abnormalities and recognized genetic disorders). Table 4 presents the results of these comparisons stratified by "pure"/"impure" status and both combined. The results indicate that exposure to valproate increased the riskfor major malformations significantly.

Table 4. Relative risks (and 95% confidence intervals) for the association between exposure to Depakote and major congenital anomalies:

	Number of Exposed Women	Number (%) of Malformations	Relative Risk (95% confidence interval)*
"Pure" prospective	123	12 (9.8)	6.02 (3.52-10.31)
"Impure" prospective	78	5 (6.4)	3.96 (1.70-9.24)
"Pure" + "Impure" prospective	201	17 (7.2)	5.22 (3.31-8.23)

* The 1.62% referent rate for malformations is the overall rate in the malformations surveillance program, after excluding recognized genetic malformations.

We also tested whether these significant findings would hold when comparing the major malformation prevalence rate in valproate-exposed women to that of women exposed to phenobarbital (a risk factor for birth defects in this data set) and to that of women exposed to 3 other commonly used AEDs. Tables 5, 6, and 7 present the comparison of demographic, exposure, and perinatal information for "pure", "impure", and "pure" + "impure" pregnancies, respectively. We include all enrolled cases, live births, stillbirths, and those having spontaneous abortions and elective terminations. As shown, valproate has a significantly higher malformation rate than the other groups in all cases. Most demographic and exposure variables, however, do not differ significantly. Therefore, the observed differences do not appear to be the consequence of any measured confounder.

Table 5. Valproate, phenobarbital, and the 3 other most commonly used AEDs in "pure" pregnancies.*

	Phenobarbital (n = 73)	Valproate (n = 142)	Other AEDs[1] (n = 619)
Child Male	32 (51.6)	63 (52.5)	292 (51.9)
Married	54 (96.4)	59 (73.8)	330 (88.7)
Mother's Education			
≤Grade 12	8 (19.1)	16 (29.1)	46 (24.1)
Some College, Junior College Graduate	14 (33.3)	11 (20.0)	44 (47.1)
College Graduate (4-year)	11 (26.2)	22 (40.0)	66 (81.7)
Post College	9 (21.4)	6 (10.9)	35 (18.3)
Maternal Age (mean, SD)	32 (5)	29 (6)	30 (5)
Gravida (mean, SD)	2.7 (1.8)	2.1 (1.2)	2.2 (1.3)
Child Caucasian	60 (82.2)	117 (82.4)	536 (86.5)
Father Caucasian	59 (80.8)	109 (77.3)	528 (85.3)
Age at First Seizure (mean, SD)	15 (8)	13 (6)	17 (9)
Seizures During Pregnancy	23 (31.5)	28 (23.1)	217 (36.1)
Prenatal Vitamins or Multivitamins	66 (90.4)	108 (77.1)	540 (87.5)
Folic Acid Supplement	38 (52.8)	96 (68.1)	392 (63.7)
Cigarette Smoking			
None	62 (84.9)	113 (79.6)	525 (84.8)
>None, <1/2 pack	3 (4.1)	6 (4.2)	28 (4.5)
≥1/2 pack, <1 pack	4 (5.5)	13 (9.2)	27 (4.4)
≥1/2 pack, <1 pack	3 (4.1)	10 (7.0)	32 (5.2)
Yes, but unknown	1 (1.4)	-	7 (1.1)
Alcohol			
None	54 (74.0)	120 (84.5)	486 (78.5)

Moderate (>none, <5 drinks/week)	15 (20.6)	19 (13.4)	122 (19.7)
≥5 drinks/week	3 (4.1)	1 (0.7)	7 (1.1)
Unknown	1 (1.4)	2 (1.4)	4 (0.7)
Child with Confirmed Major Congenital Anomaly [2]	5 (6.8)	12 (8.5)	16 (2.6)
Child's Birthweight (in grams, mean, SD)[3]	3277 (584)	3282 (653)	3402 (623)
Child's Length (in cm, mean, SD) [3]	50 (4)	51 (4)	51 (4)
Child's Head Circumference (in cm, mean, SD) [3]	34 (5)	34 (2)	35 (2)

*Numbers and proportions do not always match due to missing values. [1]The three other drugs used most often as monotherapy by enrolled women. [2]Confirmed by inspection of medical records by trained clinical dysmorphologists. [3]Excluding stillbirths and fetal deaths.

Table 6. Valproate, phenobarbital, and the 3 other most commonly used AEDs in "impure" pregnancies*.

	Phenobarbital (n = 68)	Other AEDs[1] (n = 85)	Valproate (n = 469)
Child Male	31 (48.4)	41 (52.6)	210 (47.2)
Married	48 (90.6)	41 (77.4)	160 (85.6)
Mother's Education			
≤Grade 12	6 (22.2)	8 (22.2)	26 (21.0)
Some College, Junior College Graduate	12 (44.4)	13 (36.1)	26 (21.0)
College Graduate (4-year)	4 (14.8)	11 (30.6)	44 (35.5)
Post College	5 (18.5)	4 (11.1)	28 (22.6)
Maternal Age (mean, SD)	31 (5)	30 (6)	30 (6)
Gravida (mean, SD)	2.6 (1.4)	2.3 (1.4)	2.4 (1.5)
Child Caucasian	60 (88.2)	75 (88.2)	399 (85.1)
Father Caucasian	58 (85.3)	66 (77.7)	385 (82.4)
Age at First Seizure (mean, SD)	14 (9)	15 (6)	17 (9)
Seizures During Pregnancy	24 (35.3)	28 (36.4)	185 (40.6)
Prenatal Vitamins or Multivitamins	62 (91.2)	75 (87.2)	414 (88.5)
Folic Acid Supplement	34 (50)	59 (68.6)	267 (57.3)
Cigarette Smoking			
None	56 (82.4)	67 (77.9)	409 (87.2)
>None, <1/2 pack	6 (8.8)	3 (3.5)	10 (2.1)
≥1/2 pack, <1 pack	2 (2.9)	6 (7.0)	19 (4.1)
≥1/2 pack, <1 pack	4 (5.9)	10 (11.6)	28 (6.0)
Yes, but unknown	-	-	3 (0.6)
Alcohol			
None	55 (80.9)	77 (89.5)	395 (84.2)
Moderate (>none, <5 drinks/week)	12 (17.7)	9 (10.5)	64 (13.7)
≥5 drinks/week	1 (1.5)	-	7 (1.5)
Unknown	-	-	3 (0.6)
Child with Confirmed Major Congenital Anomaly [2]	3 (4.4)	5 (5.9)	18 (3.8)
Child's Birthweight (in grams, mean, SD)[3]	3412 (469)	3380 (464)	3477 (538)

Child's Length (in cm, mean, SD) [3]	51 (2.5)	51 (3)	51 (3)
Child's Head Circumference (in cm, mean, SD) [3]	34 (2)	35 (1)	34 (2)

*Numbers and proportions do not always match due to missing values. [1]The three other drugs used most often as monotherapy by enrolled women. [2]Confirmed by inspection of medical records by trained clinical dysmorphologists. [3]Excluding stillbirths and fetal deaths.

Table 7. Valproate, phenobarbital, and the 3 other most commonly used AEDs in "pure" + "impure" pregnancies.*

	Phenobarbital (n = 141)	Other AEDs[1] (n = 237)	Valproate (n = 1088)
Child Male	63 (50.0)	104 (52.5)	502 (49.8)
Married	102 (93.6)	101 (74.8)	490 (87.7)
Mother's Education			
≤Grade 12	14 (20.3)	25 (27.2)	72 (22.9)
Some College, Junior College Graduate	26 (37.7)	24 (26.1)	70 (22.2)
College Graduate (4-year)	15 (2.7)	33 (35.9)	110 (34.9)
Post College	14 (20.3)	10 (10.9)	63 (20.0)
Maternal Age (mean, SD)	31 (5)	29 (6)	30 (6)
Gravida (mean, SD)	2.7 (1.6)	2.1 (1.3)	2.3 (1.4)
Child Caucasian	120 (85.1)	200 (85.1)	935 (85.9)
Father Caucasian	117 (83.0)	180 (76.9)	913 (84.1)
Age at First Seizure (mean, SD)	15 (8)	14 (6)	17 (9)
Seizures During Pregnancy	47 (33.3)	56 (28.0)	402 (38.0)
Prenatal Vitamins or Multivitamins	128 (90.8)	190 (81.2)	954 (87.9)
Folic Acid Supplement	72 (51.4)	161 (68.5)	659 (61.0)
Cigarette Smoking			
None	118 (83.7)	187 (78.9)	934 (85.9)
>None, <1/2 pack	9 (6.4)	10 (4.2)	38 (3.5)
≥1/2 pack, <1 pack	6 (4.3)	19 (8.0)	46 (4.2)
≥1/2 pack, <1 pack	7 (5.0)	21 (8.9)	60 (5.5)
Yes, but unknown	1 (0.7)	-	10 (0.9)
Alcohol			
None	109 (77.3)	203 (85.7)	881 (81.0)
Moderate (>none, <5 drinks/week)	27 (19.2)	30 (12.7)	186 (17.1)
≥5 drinks/week	4 (2.8)	1 (0.4)	14 (1.3)
Unknown	1 (0.7)	3 (1.3)	7 (0.6)
Child with Confirmed Major Congenital Anomaly [2]	8 (5.7)	16 (6.8)	34 (3.1)
Child's Birthweight (in grams, mean, SD)[3]	3345 (532)	3321 (586)	3436 (588)
Child's Length (in cm, mean, SD) [3]	51 (3)	51 (3)	51 (3)
Child's Head Circumference (in cm, mean, SD) [3]	34 (4)	34 (1)	34 (2)

*Numbers and proportions do not always match due to missing values. [1]The three other drugs used most often as monotherapy by enrolled women. [2]Confirmed by inspection of medical records by trained clinical dysmorphologists. [3]Excluding stillbirths and fetal deaths.

V. PREVIOUS OBSERVATIONS ON INFANTS EXPOSED *IN UTERO* TO VALPROIC ACID

Technically the earliest suggestions of the possible teratogenicity of valproic acid were the published letters-to-the-editor by Dalens et al (1) in 1980 and later, Gomez et al (2) in 1981. However, many more clinicians learned of this possibility for the first time from the letter-to-the-editor by Robert and Guibaud in the October 23, 1982 issue of Lancet (3) in which they announced their findings of which rate of spina bifida (Odds Ratio 20.6; p<.000001) among infants exposed to valproic acid during pregnancy. This observation was made from a large case-control study in the Rhone-Alpes region of France and was part of the International Clearing House for Birth Defects Monitoring. This finding prompted colleagues from other countries in the International Clearing House to review their data and confirmed quickly in a letter published in the November 13, 1982 issue of Lancet the high rate of occurrence of spina bifida after exposure to valproic acid, but not anencephaly, another common neural tube defect.

Several additional observations followed in different types of publications: case reports (5-11), case series (12), review articles (13,14), one case-control studies (15) and one prospective cohort study (16). While initial reports focused on the increased risk of spina bifida (17), subsequent studies emphasized the increased frequency of less well-known effects, such as limb reduction defects in the arms (18,19) and autism (10,11). Since the outcomes identified by the AED Pregnancy Registry will concentrate on major structural abnormalities that will have been identified at birth, the list of the potential outcomes relevant to this report are those listed in case series (12), reviews (13,14) the cohort (16) and case-control (15) studies. These include:

a) oral clefts, e.g. cleft lip and palate
b) abdominal wall defects
c) genitourinary anomalies, e.g. hypospadias
d) limb anomalies, e.g. hypoplasia of radius
e) club foot deformity
f) spina bifida

The outcomes identified among the infants born to women enrolled in the Registry who took valproic acid (Depakote) as monotherapy are consistent with the observations published previously.

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VI. CONSULTATION WITH ABBOTT LABORATORIES:

This report starts the process of review and discussion between the staff of the AED

Pregnancy Registry and the representatives of Abbott Laboratories, the manufacturer. The policy of the Registry, as established by the Scientific Advisory Committee, is to inform the manufacturer first and to allow a period of 30 days for consultation and review. The members of the Scientific Advisory Committee and the Steering committee will be notified of this finding after that 30-day period.

Please tell us how and when you would like to continue this review and discussion.

*Dr. Tennis will leave GlaxoSmithKline on September 4, 2002; her replacement has not been identified.